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ORIGINAL PAPER

Quantification of thermal ring flexibilities of aromatic and heteroaromatic compounds

Piotr Cysewski

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Abstract The consequences of thermal fluctuations occurring at room temperatures on the aromatic character of a broad group of compounds were analyzed in three distinct ways. First of all, the ring deformations were modeled along normal coordinates coming from quantum thermo-chemistry computations. The amplitudes of vibrations were estimated according to absorbed energies at room temperature. Alternatively, in-plane and out-of-plane ring deformations were modeled via scanning procedure with partial relaxation of the molecular geometry. The influence of ring deformations on π -electron delocalization was expressed in terms of HOMA values. Besides, the ring deformability was defined as the averaged change of bond angles or dihedral angles constituting the ring that was associated with $1.5 \text{ kcal mol}^{-1}$ increase of the system energy. The molecules structures adopted during vibrations at room temperature can lead to significant heterogeneity of structural index of aromaticity. The broad span of HOMA values was obtained for analyzed five- or six-membered aromatic and heteroaromatic rings. However, the averaged values obtained for such fluctuations almost perfectly match HOMA values of molecule in the ground state. It has been demonstrated that the ring deformability imposed by bond angle changes is much smaller than for dihedral

angles with the same rise of system energy. Interestingly in the case of out-of-plane vibrations modeled by scanning procedure there is observed linear correlation between ring deformability and HOMA values. Proposed method for inclusion of thermal vibrations in the framework of π -electron delocalization provides natural shift of the way of thinking about aromaticity from a static quantity to a dynamic and heterogeneous one due to inclusion of a more realistic object of analysis – thermally deformed structures. From this perspective the thermal fluctuations are supposed to be non-negligible contributions to aromaticity phenomenon.

Keywords Aromaticity · Benzene · Heteroaromaticity · HOMA · Normal coordinate analysis · Nucleic acid bases · Thermal vibrations

Introduction

The π -electron delocalization is a commonly occurring phenomenon [1–3] leading to unique physico-chemical properties of molecular systems due to characteristic structural, energetic, magnetic and reactivity consequences. There is common consensus [4–13] that aromaticity is characterized by a collection of properties of a cyclic π -electron system independent of whether the cause of aromatic stability is considered due to the π -electron or σ -electron structure. The multi-dimensionality of this quantity [14] makes the problem of quantification a non-trivial fact and despite numerous aromaticity measures that were introduced by different authors [4–14] there is no one unambiguous criterion that can be used for all molecular systems. For example one of the most widely used structural index of aromaticity, harmonic oscillator model

P. Cysewski (✉)
Department of Physical Chemistry, Collegium Medicum,
Nicolaus Copernicus University,
Kurpińskiego 5,
85-950, Bydgoszcz, Poland
e-mail: piotr.cysewski@cm.umk.pl

P. Cysewski
Department of General Chemistry,
University of Technology and Life Sciences in Bydgoszcz,
Seminarnyja 3,
85-326, Bydgoszcz, Poland

of aromaticity (HOMA) [15, 16], assumes the idea of non-alternation of chemical bonds in aromatic systems. However, bond-length alternation (BLA) is not always a univocal indicator of aromaticity as it was demonstrated by Feixas et al. [17, 18]. It has been demonstrated that significant BLA of distorted benzene structures do not affect its aromaticity measured by large negative NICS values. Aihara et al. [19] confirmed that benzene tends to stay highly aromatic and highly diatropic even if strong bond-length alternation is introduced artificially into the π -electron system and within annulene family benzene π -electron delocalization is the least sensitive to bond-length alternation. Interestingly, two decades ago Aihara [20] suggested that also aromatic stabilization energy (ASE) is quite insensitive to bond length alternation. On the other hand aromaticity is strongly associated with the rings planarity but even this feature is not a *sine qua non* condition which was documented by numerous experimental [21–26] and theoretical investigations [4–18, 27, 28]. Benzene ring can undergo large out-of-plane distortions [21–28] but its aromaticity and ring-current diamagnetism seem to be quite insensitive to such deformations of the molecule [17–30]. Even benzene itself in crystalline state at 20 K is non-planar [31] which has been attributed to intermolecular interactions in the crystal lattice. Van Zijl et al. [29] noted that meta-cyclophane is highly diatropic despite its strongly bent benzene ring and observed CC bond lengths of the ring are uniform within an experimental error. Furthermore, on the basis of the magnetic criterion of aromaticity, Rice et al. [32] reported that paracyclophanes should be classified as aromatic notwithstanding the considerable non-planar distortions of the benzene ring [31]. Polycyclic benzenoid hydrocarbons also appear to retain aromaticity even if they are heavily distorted [33, 34]. Another interesting aspect is related to reaction of aromatic compounds. Recently, Rozgonyi et al. [35] have used an unbiased *ab initio* molecular dynamics for demonstration that aromaticity remains the organizing force even at high temperature and the ground-state reaction paths continue to proceed through aromatic configuration. Furthermore, the transition state of a Diels Alder reaction between ethylene and butadiene is formally iso- π -electronic with bond-alternate benzene [36, 37]. This pericyclic transition state also exhibits a large negative NICS value at the central region and should reasonably be regarded as an aromatic specie.

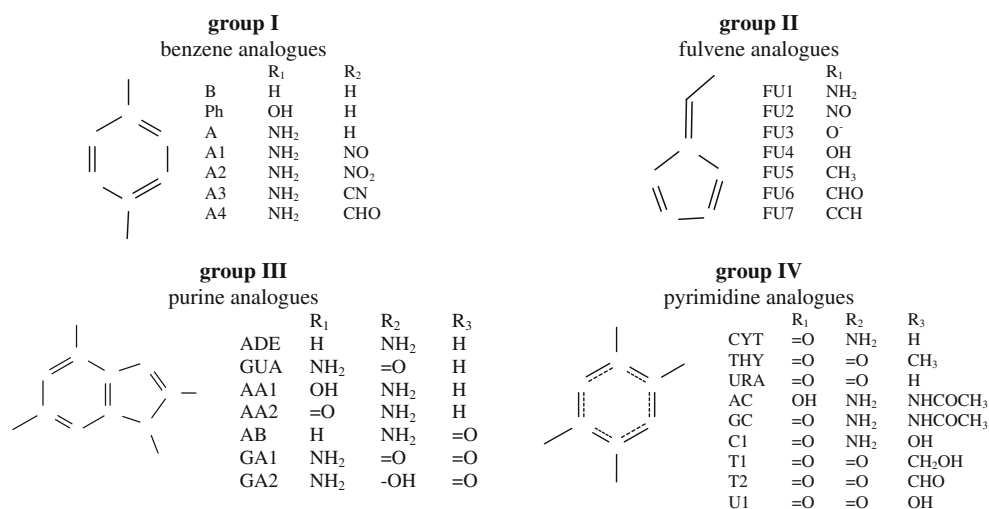
Interestingly aromatic ring elasticity was documented also as the common phenomenon not only to benzene analogues but also characteristic for heterocyclic compounds [38–43]. This is of particular importance since it provides additional degrees of freedom to biomolecules interacting in native environments. The structural non-rigidity of selected numbers of aromatic and heteroaromatic molecules has been

investigated by quantum chemical optimization and quantum chemistry molecular dynamics. Shishkin et al. demonstrated in a series of publications [38–43] that lowest-lying molecular vibrations stand for high flexibility of the aromatic rings. An energy increase between a planar equilibrium conformation and a non-planar deformed structures can be characterized by rising of the endocyclic torsion angles up to ± 20 degrees with an increase of only 1.2–1.8 kcal mol⁻¹ depending on the system [38]. This indicates that such molecular motions, even for highly aromatic compounds such as benzene or adenine, can be the source of non-trivial deformations that can potentially lead to alterations of π -electron delocalization. Despite great interest in the flexibility of aromatic and hetero-aromatic rings no systematic study was performed till now for methodical inclusion thermally available aromatic ring deformations. This paper intends to fill this gap and provides detailed analysis of in-plane and out-of-plane flexibilities of six- and five-membered rings in terms of HOMA index of aromaticity.

Methods

The subject of our investigations comprises a series of compounds possessing aromatic or heteroaromatic rings. The schematic representation of analyzed structures can be found in Fig. 1. Both five- and six-membered rings were considered. These compounds form quite a diverse set in the sense of broad range of aromatic nature. The influence of the structural flexibility on the aromatic character was quantified by means of geometric criterion (HOMA) [15, 16]. Deformations of the ring skeleton were modeled in three distinct ways. The initial geometries were fully optimized on B3LYP/6-311+G** level. The thermodynamics computations were performed for ensuring that no imaginary frequencies were assigned and obtained structures characterized ground states. Then, paths along normal coordinates were identified for each of the analyzed compounds based on Hessian estimated on the same level of theory. Both optimization and vibrational analysis was performed using Gaussian03 program [44]. For deformational analysis only those modes of vibrations were considered that are present in room temperature at least in 2% of the whole population. This corresponds to excitation energy not higher than 1.5 kcal mol⁻¹ with respect to the lowest state. The amplitudes of vibrations were estimated according to absorbed energies at 298 K. For this reason for every vibrational mode the series of structures were generated along the normal coordinate with arbitrary steps and corresponding energies were estimated by means of single point computations at the same level as frequencies computations. Then six-order polynomials were used for approximation of energy function changes along the normal

Fig. 1 Schematic representation of structures of analyzed aromatic and heteroaromatic compounds



coordinate path. This is more than enough bearing in mind harmonic character of vibrations. Based on this approximation the values of amplitudes of vibrations were obtained for the first, or in some cases for second, excitation levels. The actual excitation energies corresponded to those vibration modes that are induced at room temperature (up to 1.5 kcal mol⁻¹).

This way of modeling of molecular motions overestimates the molecular deformations due to the very nature of quantum oscillator. In the case of classical vibrations the most probable states correspond to oscillations equal to amplitudes. This is not the case for quantum vibrations for which the most probable is the ground state. Thus, alternative ways of structure deformations are also considered by adopting Shishkin approach [23, 39]. It is obvious that vibrations along normal modes can be decomposed into different structural deformations as bond or torsion angles stretching, bending, out-of-plane breathing, etc. The distribution of potential energy (PED) [45–47] in each internal coordinate is commonly used for determination of such contributions. Among them there are two of the most important deformations that seem to be crucial from the perspective of aromaticity changes. The torsion angles constituting the ring skeleton are responsible for out-of-plane distortions and similarly the in-plane deformations are dependent on the bond angle changes. At room temperature significant amount of kinetic energy is available to molecular motions and this is modeled by allowing for partial relaxation of molecule coordinates. Thus, a series of geometry optimizations were performed with fixing of only one coordinate and allowing for relaxation of the remaining parts. In this procedure each of six (or five) bond or torsion angles constituting the ring were kept frozen and the rest of molecule was allowed to relax. The extension of scanning along such coordinate was controlled by energetic criterion and expansion of in-plane or out-of-plane deformations was continued until 1.5 kcal mol⁻¹ increase of energy was achieved. The averaged values of

bond angles or dihedrals corresponding to such energy increase were used as the measure of the ring deformability (RD). It is worth mentioning that the proposed scanning procedure does not include all possible in-plane deformations since there are some modes that do not involve bond angle changes of the ring. For example in the case of benzene molecule for b_{2u} symmetry or the breathing mode of a_{1g} symmetry there are active clamping deformations of hydrogen atoms (or in general side groups). These modes were not studied as separate items, since they were included in the first approach.

Results and discussion

The influence of molecular vibrations on structural index of aromaticity was studied for compounds presented in Fig. 1. There were chosen four distinct groups of structures for preserving high diversity of aromaticity. Due to different substituents connected to the rings the considered compounds can significantly differ in aromatic character. This also allows for analysis of the influence of side groups on the ring flexibility. Indeed the span of HOMA values corresponding to optimized geometries ranges from 0.465 (thymine) up to 0.989 (phenol) for six-membered rings and from -0.403 (NO-fulvene) up to 0.871 (imidazole ring of guanine), for five-membered rings, respectively. Benzene analogues (group I) and fulvene derivatives (group II) represent typical carbon-based rings while heteroaromatic compounds were included in group III (purines) and group IV (pyrimidines).

In the first part the influence of thermal vibrations on aromaticity was estimated according to three procedures described in the methodology section. Then the relationships between HOMA values and ring deformability are discussed. For illustrational purposes more examples of structural deformations of aromatic ring are provided for cyclophanes

compounds family. Finally, the correlation between obtained here heterogeneities of rings aromaticities imposed by thermal fluctuations with standard way of aromaticity assessments is presented and discussed.

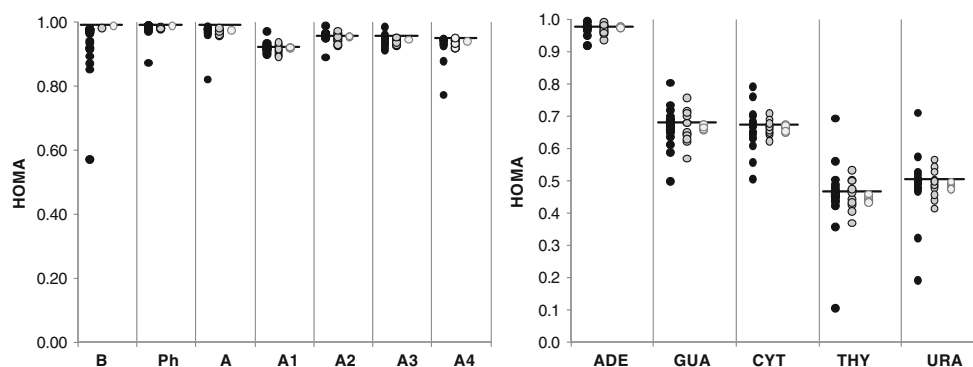
Rings structure affected by thermal vibrations

The distribution of HOMA values corresponding to three alternative models of ring vibrations were presented in Fig. 2 for selected and most representative structures defined in Fig. 1. The same scale was used for analogues of benzene and nucleic acid bases. All values of structural index of aromaticity are related to conformations that are destabilized by at most 1.5 kcal mol⁻¹ from the ground state. As it is documented in Fig. 2 each of analyzed compounds is characterized by a set of HOMA values of varying range. Usually the less aromatic compound the higher diversities of structural index of aromaticity is observed. Among three ways of the molecular motions modeling the deformations obtained along normal coordinates introduce the highest heterogeneity of HOMA index. Even benzene has some modes of vibrations that are associated with serious reduction of its aromaticity. For example 13 mode of vibration leads to occurrence of a triangle-like structure. This can impose serious linearization of every second bond-angle of the ring and consequently reduce the HOMA value down to 0.765 if considered amplitude of vibration corresponds to absorption of 1.48 kcal mol⁻¹ of energy. There are 3% of such structures at room temperature. The third mode of vibration of benzene corresponds to occasional trapezoid-like structure formation in 7% amount with reduction of HOMA value down to 0.912. However, it is worth mentioning that IR intensities of both modes are very low and corresponding peaks are not present in the infra red spectrum due to the lack of dipole moment changes. Similar patterns can also be found for other benzene analogues. On the other hand most of aromatic compounds can also gain their aromaticity as a result of vibrations along normal coordinates. A very spectacular example can be found for thymine and uracil, which both are

considered as ultra low aromatic compounds. For example 13 modes of vibration of thymine corresponds to symmetric in-plane breathing with significant increase of N₁-C₂ and C₄-C₅ bond lengths. This is accomplished with a rise of HOMA values up to 0.692, which stands for an almost 50% increase of aromaticity with respect to canonical structure. There are about 3% of such conformations in the total population. In the case of 2% of uracil conformations there are observed out of plane vibrations of C₄-C₅-C₆-N₁ torsion angle that lead to increase of HOMA values up to 0.572 with only 1.4 kcal mol⁻¹ rise of the total energy. Similar modes can be found for other considered molecules. Thus, due to low energy penalty the deformations of molecular structure imposed by intrinsic vibration modes can significantly alter planar and symmetrical structure of the ring affecting aromatic characters expressed in terms of HOMA index. Similar patterns can also be observed for higher modes, that are not available to molecular motions at room temperature. Thus, one can speculate that irradiation of molecule with specific wave length can alter aromatic character by promoting fraction of particular conformation in the whole population. Such modes of vibration, which reduces aromaticity, are expected to be less important from the reactivity point of view and only have influence on the averaged value of aromaticity. However, these modes which lead to increase of HOMA values might be responsible for more aromatic reactivity than can be deduced from the ground state conformation and may potentially be involved in speeding up of substitution reactions of vibrating molecules at any, not only room temperature.

In Fig. 2 there are also presented in-plane and out-of-plane rings deformations with inclusion of relaxation energy. The first and direct conclusion is that obtained distributions of HOMA values are much more contracted than ones obtained from normal coordinate analysis. Especially relaxation of molecular geometry accomplished with out-of-plane ring distortions can be easily diminished by mutual changes of other geometric molecular coordinates. The modification of one of dihedral angles is accomplished with alterations in opposite direction of two neighboring torsion angles of the

Fig. 2 The heterogeneity of aromatic character induced by thermal vibrations (black circles), in-plane deformations (gray circles) and out-of-plane distortions (open circles). All geometry alterations correspond to increase of system energy not extending 1.5 kcal/mol



ring if geometry relaxation is allowed. Thus, ring flexibility need not directly lead to strong variation of HOMA values if partial optimization is allowed. However, even in this model majority of aromatic compounds are characterized by relatively broad sets of HOMA values. Especially hetero-aromatic compounds are sensitive to changes of bond and torsion angles. For example in case of guanine the reduction of $C_2-N_3-C_4$ or $N_3-C_4-C_5$ bond angle by about 5° from the canonical form leads to an increase of aromatic character up to 0.710 with only $1.5 \text{ kcal mol}^{-1}$ raise of the total energy.

In order to quantify the elasticity of aromatic ring the mean values of bond angles or torsion angles constituting the ring were estimated for each of analyzed compounds. The same energetic criterion was applied in each case. The resulting values are termed ring deformability (expressed in degrees) and are presented in Fig. 3, where data for all four analyzed sets of compounds are included. Both in-plane and out-of-plane deformations were averaged over all parameters defining the ring for structures obtained after scanning procedures or normal coordinate following. Thus, the size of the ring defined the number of angles and dihedrals for averaging. Consequently, the higher value of ring deformability the stronger ring deformations are allowed with the same energy rise. Interestingly, as it can be seen in Fig. 3 the highest ring flexibility is observed for out-of-plane distortions if relaxation of the remaining coordinates is allowed. However, the values of RD are almost the same for all of analyzed benzene analogues and slightly exceed 14° . For heterocyclic compounds much stronger relationship with aromaticity is observed and usually increase of ring deformability is correlated with decrease of aromatic character. It is interesting to see if there is any correspondence between ring deformability and HOMA values. This is demonstrated in Fig. 4. In all analyzed cases the in-plane deformations are much smaller irrespectively of the way of modeling of thermal vibrations. Apparently, there is quite acceptable relationship (with

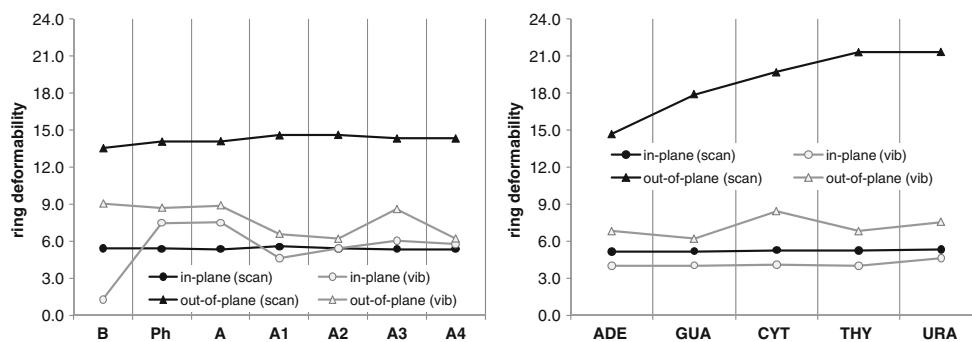


Fig. 3 The ring deformability (RD are expressed in degrees) corresponding to averaged values of bond angles or torsion angles changes that were correlated with $1.5 \text{ kcal mol}^{-1}$ increase of energy

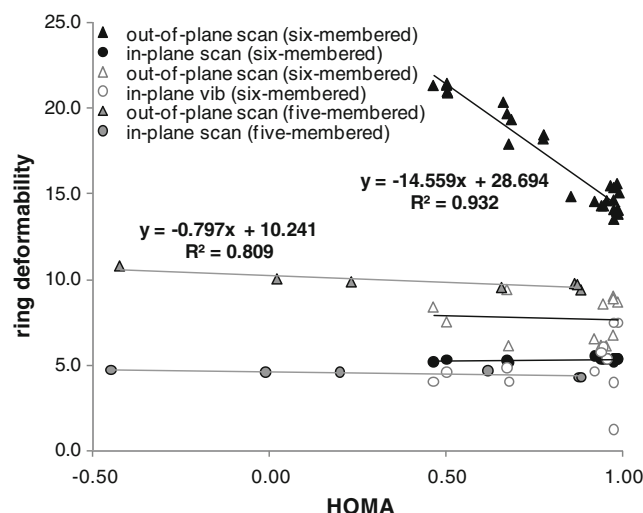


Fig. 4 The ring deformability (expressed in degrees) corresponding to averaged changes of bond angles or torsion angles associated with not higher than 1.5 kcal/mol energy increase with respect of the ground state

correlation coefficient exceeding 0.93) between structural index of aromaticity and six-membered ring deformability obtained during scanning procedure. Also out-of-plane deformability of five-membered rings resulting from scanning procedure can be correlated with HOMA vales, although the correlation coefficient is slightly smaller in this case ($R^2=0.81$). For other cases there is no correlation between ring elasticity with structural index of aromaticity. The averaged in-plane deformations via geometry scanning as well as all deformability obtained along normal coordinates are almost the same irrespectively of ring size and its aromatic character. For example averaged values of bond angles constituting the ring are close to 5° irrespectively of the ring type. The only exception is observed in the case of benzene, for which this values is much smaller and equals 1.3° . Interestingly, the lack of correlation with aromaticity is also observed for out-of-plane vibrations for five-membered rings. The spectrum of analyzed rings is

from the ground state of aromatic or heteroaromatic compounds. In-plane vibrations are defined as bond angle changes, while torsion changes are responsible for out-of-plane fluctuation

quite extended since it encompasses both anti-aromatic compounds as some fulvenes and highly aromatic imidazole rings in purines. Thus, it seems that ring flexibility is directly correlated with aromaticity only for six-membered aromatic and heteroaromatic rings if partial geometry relaxation is allowed.

Deformability of distorted benzene rings

The ring deformability can be even more pronounced by analysis of structural properties of cyclophanes [36]. This interesting group of compounds is well-studied [37, 38] in organic chemistry because they adopt unusual chemical conformations due to build-up aromatic unit and an aliphatic chain that forms a bridge between two non-adjacent positions (typically para or meta) of the aromatic ring. Some of derivatives possess two *p*-phenylene groups held face to face by $-\text{[CH}_2\text{]}_n-$ bridges. The interesting thing about cyclophanes is that they are forced to adopt unusual chemical conformation of aromatic ring due to steric restrictions of the build-up chain. In this respect they are ideally suited for the purpose of this paper and can serve as interesting illustration of the very nature of six-membered aromatic ring. The full gradient optimization was performed for series of three types of cyclophanes. Resulting correlation between aromaticity and ring deformability along with chemical structures are presented in Figs. 5 and 6. It is worth mentioning that ring deformability coming from averaged bond angle and torsion angle constituting the ring do not come this time from distorted but rather optimized structures. From Fig. 5 it is clearly visible that structures,

Fig. 5 The correlation HOMA values and out-of-plane phenyl ring deformations in a variety of cyclophane systems

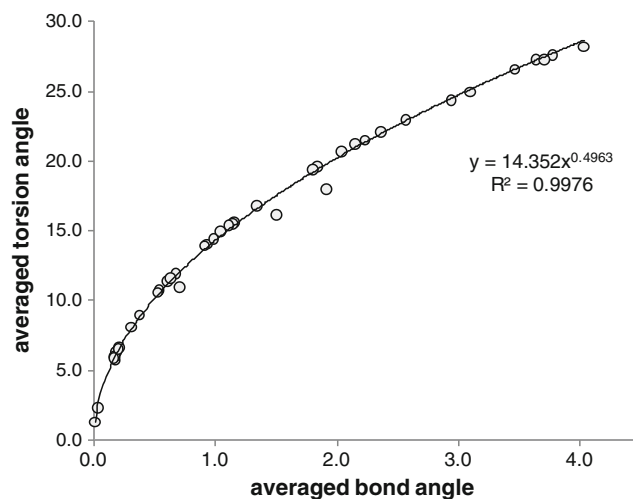
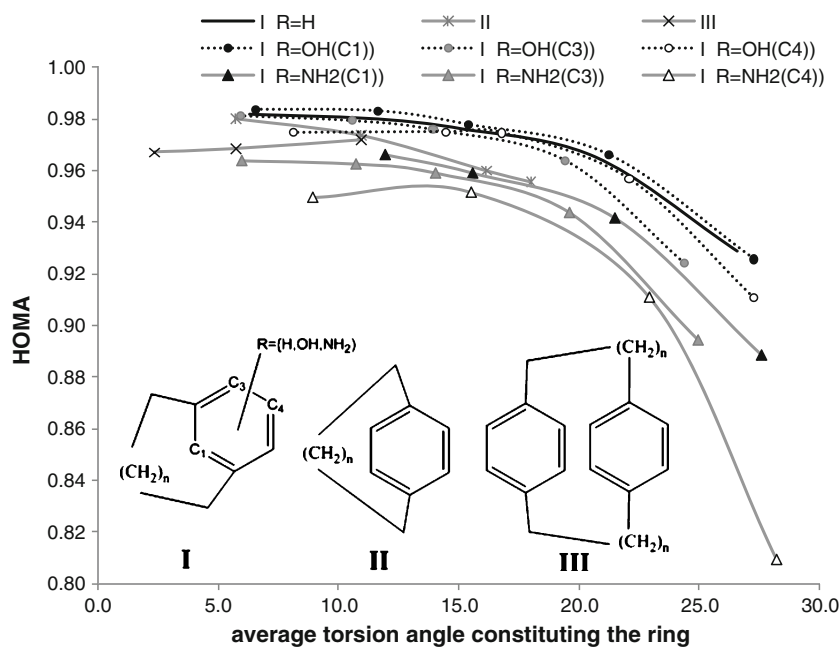


Fig. 6 The correlation between in-plane and out-of-plane deformations for optimized structures of different cyclophanes analogues (see Fig. 5 for chemical structures)

which possess out-of-plane deformation up to 15° are practically as aromatic as benzene itself. Within this scope of ring deformability there is fairly linear correlation between HOMA values and mean torsion angles constituting the ring. Exceeding deformations of the ring beyond this value imposes significant reduction of π -electron delocalization and correlation becomes non-linear. The ring deformation with respect to bond angles and torsion angles are related to each other, although this correlation is not linear as it is presented in Fig. 6. Again the resistance of the ring toward in-plane distortions is much higher if compared with out-of-plane deformations. Interestingly presence of

amino- or hydroxyl- side groups does not change these conclusions irrespectively of their position in the cyclophane ring.

Quantifications of aromaticity fluctuations

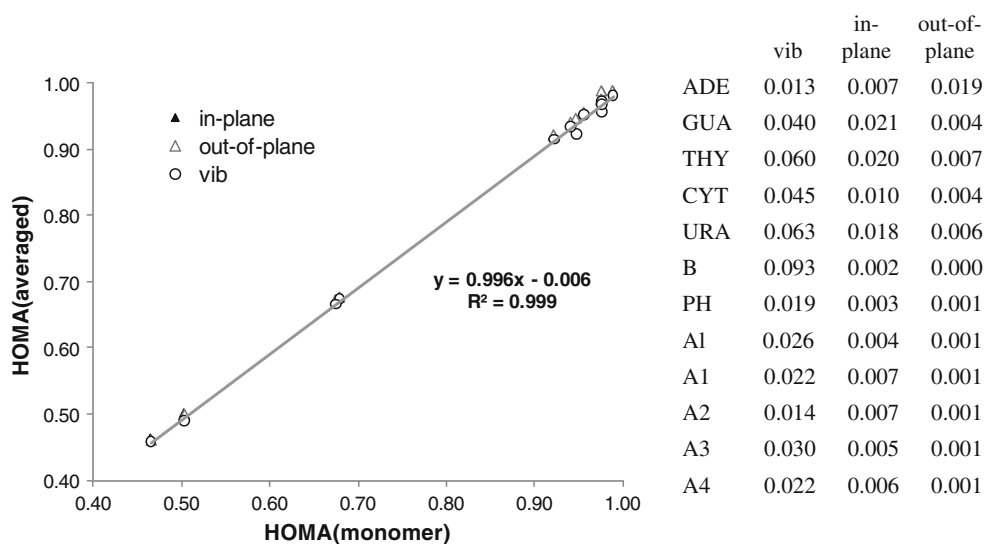
The above discussed data suggest that significant heterogeneities of ring aromaticities can be imposed by thermal vibrations. Although modeled out-of-plane fluctuations have quite a small influence on the HOMA values if relaxation of the geometry is allowed, there are still non-trivial distributions of this index for many aromatic compounds. It is interesting to see if there is any correlation between HOMA values that are commonly obtained based on the ground state geometry and averaged ones coming from the considered here series of structures. For proper estimation of average values of aromaticity index for modeled thermal fluctuations, the percentage of particular structure in the whole population must be taken into account. Thus, the standard deviation (SDV) expressed as the square root of population variance were estimated after summing up all values corresponding to structures within $1.5 \text{ kcal mol}^{-1}$ with weighting factor obtained based on Boltzmann probabilities at room temperature. The results corresponding to all three ways of modeling of thermal vibrations were presented in Fig. 7. It clearly documents that at room temperature there is perfect correlation between aromaticities averaged over thermal fluctuation and coming from the ground state structure. The close to unity value of R^2 suggests that ground state conformations although corresponding to zero Kelvin temperature, hence not present in the real population at any temperature, is a very good representation of properties of aromatic compounds. Although ignoring of the thermal fluctuations in the description of aromaticity does not change the mean

values of structural index of aromaticity and leads essentially to the same quantity there is a sense in using representative spectrum of conformations. Such an analysis can provide the magnitude of variability of the aromaticity index. Thus, provided here analysis extends the traditional understanding of aromaticity. Fortunately the values of SDV for HOMA are quite small as can be seen in Fig. 7. However, the SDV values can very rapidly increase if the temperature rises.

Conclusions

Although aromaticity is a commonly used term its multidimensional character and enumerative nature make its application and interpretation a non-trivial task. This is proved by the enormous number of papers published every year that address this old phenomenon. Usually conjunction of several prepositions are used that must be inclusively fulfilled. Among them the most commonly accepted assumes that aromaticity is correlated with the higher energetic stability (in comparison to non-aromatic analogues), the π -electron delocalization expressed in terms of non-alternation of bond lengths (or related properties as bond orders, electron densities at bond critical points, etc.), ring critical points characteristics or magnetic susceptibilities and also as higher reactivity toward substitution rather than addition reactions. However, all these aspects are mainly related to the ground state that corresponds to the global minimum on the configuration hyperspace. It is obvious that real molecules possess many more degrees of freedom that might potentially affect its aromaticity. In this paper one of such aspects is discussed and importance of series of structures corresponding to thermal fluctuations is suggested. This can be an important factor affecting aromaticities. The first

Fig. 7 Correlation between HOMA values characterizing ground state and mean value of thermally excited geometries at room temperature. Values of SDV (standard deviation of population variance) were also provided



observation is that the molecular structures adopted during vibrations at room temperature can lead to significant heterogeneity of structural index of aromaticity. The averaged values obtained for such fluctuations almost perfectly match HOMA values of molecule in the ground state. Although ignoring of the thermal fluctuations in the description of aromaticity does not change the mean values of structural index of aromaticity and leads to essentially the same quantity, the distribution of aromaticity indices can be available. This extends the traditional understanding of aromaticity. The standard deviation expressed as the square root of population variance (SDV) which includes Boltzmann probabilities is small for highly aromatic compounds and increases with reduction of aromaticity. The deformability of the ring imposed by thermal fluctuations can also be expressed as the mean change of bond angles or torsion angles constituting the ring that are correlated with a given increase of the system energy. Here the arbitral value of 1.5 kcal mol⁻¹ level was used since such energy increase can be observed for at least 2% of vibration structures at room temperature. The proposed measure of ring resistance to structure deformation is expressed in degrees. It has been demonstrated that the ring deformability imposed by bond angle changes is much smaller than for dihedral angles with the same rise of system energy. Interestingly only in the case of out-of-plane vibrations modeled by scanning procedure lead to linear correlation with HOMA index. Proposed in this paper method for inclusion of thermal vibrations in the framework of π -electron delocalization provides natural extension of the way of thinking about aromaticity from static quantity to dynamic and heterogeneous one for inclusion of a more realistic object of analysis. From this perspective the thermal fluctuations are supposed to be non-negligible contributions to aromaticity phenomenon.

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